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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,580	04/02/2001	Michael J. Eppihimer	08702.0006-00000	9952

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/825,580	EPPIHIMER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,25-27,29-40 and 43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 25-27, 29-40 and 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Reply Brief filed on 12/17/2007, PROSECUTION IS HEREBY REOPENED.

New Grounds of Rejections are set forth below.

Applicant's Reply Brief, filed 12/17/2007, noted that the Examiner's Answer did not state the rejection of claim 27 under 35 USC 103(a) as unpatentable over Cummings, Larsen, Blann, Araneo, DeFrees, the Merck Manual, Lip further in view of Maugeri and Johnston stands.

It appears that the Examiner's Answer followed the Grounds of Rejection set forth in Section VI in the Appeal Brief, filed 07/06/2007.

This Office Action provides for this rejection of record and adds additional references to provide further support for the rejections of record.

The examiner apologizes for any inconvenience to applicant in this matter.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

2. Claims 1-20, 25-27, 29-40 and 43-57 are pending.

Claims 21-24, 28, 41 and 42 have been canceled previously.

The election of the species "hypertension" has been acknowledged.

Upon a review of the prosecution of the instant application, it has been noted that applicant initially elected the species hypertension when it was recited as a member of a Markush.

Subsequent to the original election, applicant amended the claims to recite "hypertension" in the independent claims.

In order to avoid confusion based upon the original election of species and the current recitation of the claims and in the interest of compact prosecution,

the election of species has been extended to the previously withdrawn claims.

Claims 1-20, 25-27, 29-40, 43-57 are under consideration as they read on the elected species, hypertension, given the recitation of "hypertension" in the independent claims and in the interest of compact prosecution.

3. This Action will be in response to applicant's Reply Brief, filed 12/17/2007.

The rejections of record can be found in the previous Office Actions.

Applicant's arguments, in conjunction with the Hemmerich 132 Declaration, filed 09/13/2006, and the examiner's rebuttal are essentially the same as of record.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in the previous Office Actions. For example, see the Office Actions, mailed 03/17/2005, 09/07/2005, 03/14/2006 and 10/18/2007.

Further, New Grounds of Rejection have been set forth herein.

4. As indicated previously, the priority date of the instant claims is deemed to be the filing date of the instant application USSN 09/825,580, filed 4/2/2001, as the previous priority application USSN 60/193,787, filed 3/31/00, does not support the claimed limitations of the instant application, encompassing "methods of treating or inhibiting thrombosis in a subject having hypertension … (a) – (f)" , all of the limitations of the "PSGL-1 protein or fragment thereof" including "SEQ ID NO: 2", the "dosing" (e.g. see instant claims 18-20) and "modes of administration" (e.g. see claim 17) and "targeted diseases", currently claimed.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112, first paragraph.

5. The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. This is a New Grounds of Rejection.

Claims 31-40 and 43-57 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The following grounds of enablement rejection pertain to preventing deep vein thrombosis a prophylactic method of treating or inhibiting thrombosis.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively prevent deep vein thrombosis or prophylactically treat or inhibit thrombosis in subjects (e.g., humans) by administering PSGL-1 of the present invention. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations with the pharmaceutical composition comprising the antibody to the development of effective methods of preventing deep vein thrombosis or prophylactically treating or inhibiting thrombosis in subjects.

Prevent means to keep from happening or occurring

A prophylactic is a medication or a treatment designed and used to prevent a disease from occurring.

It is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Inhibiting receptor-ligand interactions is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as deep vein thrombosis or thrombosis targeted by the claimed invention.

In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission.

Generally, such diseases are diagnosed only after significant tissue damage has occurred.

According, to The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999) (892 mailed 03/17/2005; of record);
primary hypertension is of unknown etiology (e.g., see Etiology and Pathogenesis on page 1632) and is asymptomatic (e.g., see Symptoms and Signs on pages 1632-1633) and secondary hypertension is associated with various diseases and the use of various agents (e.g., see Secondary Hypertension on page 1632).

The instant disclosure does not provide sufficient in vitro or in vivo evidence showing that the administration of PSGL-1 can counteract the cause or the manifestations of deep vein thrombosis or thrombosis in order to prevent or to prophylactically treat/inhibit these conditions.

Furthermore, it is noted that, under the broadest reasonable interpretation, a method for preventing congestive heart failure broadly encompasses a target population of those who do not necessarily have deep vein thrombosis or thrombosis.

Therefore, one of skill in the art would not know how to practice the claimed invention without undue amount of experimentation because one of skill in the art would not know who appropriate patient population to which target the claimed invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to prevent or to prophylactically treat/inhibit deep vein thrombosis or thrombosis and in view of lack of sufficient working examples provided by applicant of using PSGL-1, undue experimentation would be required to practice the claimed methods of preventing or to prophylactically treating/inhibiting deep vein thrombosis or thrombosis with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for preventing or to prophylactically treating/inhibiting deep vein thrombosis or thrombosis encompassed by the claimed methods.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to amend the claims to avoid the recitation of "preventing" and "prophylactic" to obviate this rejection.

Under the broadest reasonable interpretation of the claims and consideration of applicant's intent, these claims are being read as "methods of treating / inhibiting" for prior art purposes.
Here, too, "preventing" and "prophylactically treating" would be considered methods of treating patients susceptible to thrombosis / deep vein thrombosis (e.g., a patient undergoing surgery) or a patient prior to cardiovascular surgery (e.g., angioplasty).

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Given that the claims drawn to the methods of treating deep vein thrombosis have been acted upon in the instant application, the following New Grounds of Rejection have been set forth.

Claims 1-15, 17-20, 16-18, 25-27, 31-40 and 44-57 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Eppihimer et al. (Journal of Leukocyte Biology (Suppl.): 27, 1999) (1449; #E2) (see entire document).

Given the lack of clarity as the priority of all of the instant claims, this rejection is set forth under 35 U.S.C. § 102(a)(b).

Eppihimer et al. teach the role of recombinant forms of PSGL-1 in the treatment of deep vein thrombosis in a subject undergoing a surgical procedure (see Abstract).

Although the reference is silent about the structure of the recombinant form of PSGL-1 and "hypertension" per se, appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Hypertension associated with deep vein thrombosis as disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating deep vein thrombosis with PSGL-1 at the time the invention was made. Also, the prior art teaches effective dosing of PSGL-1 that anticipates the instant effective amounts.

Although the reference is silent about "a subject having hypertension" per se, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons.

Here, the prior art is based upon co-inventor's own work.

Therefore, applicant can provide the evidence of the nature and relationship of the recombinant PSGL-1 as compared to the instant claims.

10. Given that the claims drawn to the methods of treating deep vein thrombosis have been acted upon in the instant application, the following New Grounds of Rejection have been set forth.

Claims 1-20, 25-27, 31-40 and 44-57 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Eppihimer et al. (Arterioscler. Thromb Vasc Biol. 20: 2483-2488, 2000) (1449; #Journal of Leukocyte Biology (Suppl.): 27, 1999) (1449; #A14) (see entire document).

Given the lack of clarity as the priority of all of the instant claims, this rejection is set forth under 35 U.S.C. § 102(a)(b).

Eppihimer et al. teach the role of recombinant forms of PSGL-1 in the treatment of deep vein thrombosis, as well as being an effective treatment for patients at risk of adverse thrombotic events (see Abstract, Introduction Results and Discussion).

Although the reference is silent about the structure of the recombinant form of PSGL-1 and "hypertension" per se, appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Hypertension associated with deep vein thrombosis as disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating deep vein thrombosis with PSGL-1 at the time the invention was made. Also, the prior art teaches effective dosing of PSGL-1 that anticipates the instant effective amounts.

Although the reference is silent about "a subject having hypertension" per se, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons.

Here, the prior art is based upon co-inventor's own work.

Therefore, applicant can provide the evidence of the nature and relationship of the recombinant PSGL-1 as compared to the instant claims.

11. Claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53 and 57 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Cummings et al. (U.S. Patent No. 5,464,778) (see entire document) and as further evidenced by The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999) (892 mailed 03/17/2005) and Lip (Journal of Human Hypertension 14: 687-690, 2000) and Bansal et al. (Journal of the Indian Medical Association 97: 226-233 (1999) essentially for the reasons of record.

Applicant's arguments, filed in the Brief on Appeal, filed 04/27/2007, and in the Reply Brief, filed 12/17/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments, in conjunction with the Hemmerich 132 Declaration, filed 09/13/2006, and the examiner's rebuttal are essentially the same as of record.

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. See Schering Corp. v. Geneva Pharm. Inc., 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

When considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure.

There is no "manipulative difference in the method steps" between Cummings et al. and the claimed invention because both describe the administration of the same PSGL-1 to treat the same or nearly the same cardiovascular pathologies and conditions (including atherosclerosis and stroke (e.g., see Clinical Applications on columns 18-21).

Cummings et al. clearly teach that PSGL-1 would useful in the treatment of inflammatory and thrombotic disorders (e.g., see column 17, lines 60-63), in the inhibition of P-selectin-mediated interactions and leukocyte-mediated inflammation, which involved the activation of platelets and endothelium by thrombin and cytokines (e.g., see Clinical Applications on columns 18-21).

Cummings et al. clearly teach the role of platelet-leukocyte interactions in atherosclerosis, as it relates to atherogenesis (i.e., the formation of atheromas or atheromatous plaques, that is a deposit or degenerative accumulation of lipid-containing plaques, on the walls of arteries as in atherosclerosis) (e.g., see columns 19-20, overlapping paragraph).

Inhibiting thrombosis or atherogenesis in subject have hypertension would be an inherent result or benefit of Cumming's prophylactic administration of soluble PSGL- 1 to a patient with the same or nearly the same targeted diseases/conditions whether or not that benefit was recognized by Cummings et al.

It is irrelevant whether Cummings et al. methods were recognized in the art as treating or inhibiting thrombosis in subjects having hypertension, as long as treating or inhibiting "is the 'natural result flowing from' the explicit disclosure of the prior art".

As noted by the Introduction of Lip,
hypertension is/was a well-established risk factor for various diseases, including atherosclerosis and stroke and
the basic underlying pathophysiological processes underlying both of these major complication of hypertension are thrombogenesis and atherogenesis. (e.g., see Introduction of Lip).

In teaching Hypertension and Cerebrovascular Disease, newly added evidentiary reference Bansal et al. that several risk factors increase the chances of stroke but hypertension remain the single most important treatable risk factor in all age groups (e.g., see entire document, including Abstract and page 227, paragraph 2 and Conclusion).

Applicant has not identified any manipulative difference between Cummings et al. methods and the claimed methods, and therefore have failed to establish that treating or inhibiting thrombosis patients having hypertension would not have naturally or inherently flowed
from practicing Cummings et al. methods to inhibit leukocyte-platelet interactions and P-selectin-mediated interactions in order to treat various inflammatory or thrombotic conditins or disorders, including atherosclerosis and stroke,
wherein the basic underlying pathophysiological processes underlying both of these major complication of hypertension are thrombogenesis and atherogenesis

Applicant further contends that there is no recognition in Cummings et al. that a P-selectin inhibitor can function to inhibit hypertension. This argument is not persuasive. Cummings et al. describes administration of the same P-selectin inhibitor required by the claims (PSGL-1), in the same amount. Again, it is irrelevant whether Cummings et al. recognized this particular natural or inherent result of the prior art methods to inhibit thrombosis in a subject having hypertension.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

While it is acknowledged that not all patients who have hypertension have atherosclerosis, strokes and ischemia-reperfusion injuries
and that not all patients who have atherosclerosis, strokes and ischemia-reperfusion injuries have hypertension,
clearly many/most, if not all, patients with atherosclerosis, strokes and ischemia-reperfusion injuries have complications due to hypertension.

Given that the prior art teaches treating all patients with atherosclerosis, strokes and ischemia-reperfusion injuries and

given that thrombus formation and hypertension were known complications of these patients;

the prior art methods clearly taught inhibiting thrombosis in subjects having hypertension.

Thrombus formation and hypertension were not considered insignificant, trivial nor irrelevant complications of atherosclerosis, strokes and ischemia-reperfusion injuries.

The following is reiterated for applicant's convenience.

Cummings et al. teach the use of PSGL in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury, atherosclerosis and strokes (see column 18, paragraphs 5-8; columns 19-20). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3).

Although the reference is silent about "hypertension" per se, appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Cummings et al. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various conditions such as ischemic-reperfusion injury, atherosclerosis and strokes with PSGL and fragments thereof and the properties of said PSGL and fragments thereof at the time the invention was made.

Given the referenced treating of various conditions associated with thrombotic complications and in particular, ischemia-reperfusion injuries, atherosclerosis and strokes, it would have been inherent that such patients would have been identified as being subjects at risk of thrombosis. Cummings et al. also teach dosage ranges (e.g. 0.2 to 30 mg/kg body weight) for the treatment of said disorders (column 21, paragraph 1). Although this paragraph discloses carbohydrate inhibitors, the ordinary artisan would have immediately envisaged that this broad dosage range would have included other inhibitors (e.g. column 18, paragraph 4) as dictated by the specific condition (column 21, paragraphs 2-3). Also, given the nature of the specific conditions of, ischemia-reperfusion injuries, atherosclerosis and strokes, one of ordinary skill at the time the invention was made would have provide the PSGL prior to thrombus formation in subjects having hypertension.

Although the reference is silent about "a subject having hypertension" per se, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

As pointed out previously, it has been noted that treating cardiovascular diseases and conditions such as "atherosclerosis" is consistent with the instant specification (see pages 6-7, overlapping paragraph and the Section on Prophylactic And Therapeutic Methods on page 32 of the instant specification).

Further, The Merck Manual notes that arterial hypertension is a complication of atherosclerosis, cerebrovascular insufficiency with stroke and renal failure (see page 1632, Symptoms and Signs; see Atherosclerosis on pages 1654 - 1658, including page 1656, Hypertension; Cerebrovascular Disease on pages 1417-1424).

Also as noted previously, while appellant / Declarant note that prior art targeted patient populations do not necessarily have or develop hypertension, one of ordinary skill in the art would have immediately envisaged at the time the invention was made that the prior art treatment of ischemia-reperfusion injury, atherosclerosis and strokes was targeting patients with hypertension, including given the prior art teachings of treating the same patient populations as described by the instant specification.

As pointed out previously, and consistent with the Background of the Invention and disclosure of the instant specification concerning hypertension,

the Merck Manual notes that

"Hypertension is the most important risk factor predisposing to stroke";

"It is one of three risk factors, along with cigarette smoking and hypercholesterolemia predisposing to coronary atherosclerosis";

(see Prognosis on page 1634, column 1.

"Hypertension is a more important risk factor for stroke than for atherosclerotic heart disease

(see page 1632, column 1, paragraph 1 of Pathology); and

"Heart failure, symptomatic coronary atherosclerosis, cerebrovascular disease and renal failure require urgent and judicious antihypertensive therapy

(see page 1634, column 2, paragraph 1 of Antihypertensive drug therapy).

As noted by Lip, Journal of Human Hypertension,

"hypertension is well-recognized to be an important contributor to heart attacks and stroke" and that "hypertension it thrombotic in nature".

See entire document, particularly the Introduction on page 687.

This teaching by Lip is consistent with page 1, paragraph 3 in the Background of the Invention of the instant specification notes that:

"Moreover, one of the basic pathophysiological processes underlying the major complications of hypertension (i.e. heart attack and stroke) is thrombogenesis (Lip (2000) J Hum Hypertension 14:687)."

On this record, it is reasonable to conclude that the same patient(s) is (are) being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that appellant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Again and in contrast to appellant's / Declarant's statements, the record is clear that the missing descriptive matter of "a subject having hypertension" was necessarily present in the targeted patient populations and/or immediately envisaged as target populations ordinary artisan would have, given that "hypertension" was the an important if not the most important risk factor predisposing said conditions and that said targeted populations are consistent with appellant's own disclosure as filed.

Applicant's arguments have not been found persuasive.

12. Given the extension of the election of species, this New Grounds of Rejection has been set forth.

Claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53 and 57 are rejected under 35 U.S.C. § 102(e) as being anticipated by Wagner et al. (US 2002/0040008 (see entire document) and as further evidenced by The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999) (892; mailed 03/17/2005) and Lip (Journal of Human Hypertension 14: 687-690, 2000).

Wagner et al. teach the use of PSGL-1 and chimeric constructs thereof (e.g., see paragraphs [0025]-[0036] and Claims) in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including atherosclerosis and patients undergoing angioplasty, stenting procedures, atherectomy, bypass surgery or vessel-corrective techniques to aid in the prevention of restenosis (e.g., see paragraphs [0007]-[0012], [0015]-[0017], [0025], [0043] and Claims) as well as the administration and monitoring according to one of ordinary skill in the art and the needs of the patient (e.g., see paragraphs [0037]-[0047]).

Although the reference is silent about "hypertension" per se, appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Wagner et al. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various conditions such as atherosclerosis and cardiovascular procedures (e.g., angioplasty) with PSGL-1 and fragments thereof and the properties of said PSGL-1 and fragments thereof at the time the invention was made.

Although the reference is silent about "a subject having hypertension" per se, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

Treating cardiovascular diseases and conditions such as "atherosclerosis" and patients undergoing cardiovascular procedures (e.g., angioplasty) is consistent with the instant specification (see pages 6-7, overlapping paragraph and the Section on Prophylactic And Therapeutic Methods on page 32 of the instant specification).

Further, The Merck Manual notes that arterial hypertension is a complication of atherosclerosis, cerebrovascular insufficiency with stroke and renal failure (see page 1632, Symptoms and Signs; see Atherosclerosis on pages 1654 - 1658, including page 1656, Hypertension; Cerebrovascular Disease on pages 1417-1424).

This teaching by Lip is consistent with page 1, paragraph 3 in the Background of the Invention of the instant specification notes that:

"Moreover, one of the basic pathophysiological processes underlying the major complications of hypertension (i.e. heart attack and stroke) is thrombogenesis (Lip (2000) J Hum Hypertension 14:687)."

On this record, it is reasonable to conclude that the same patient(s) is (are) being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that appellant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

13. Claims 1-20, 25-40 and 43-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. Patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) AND Wagner et al. (US 2002/0040008)

in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207)

and in further evidence of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999) (892 mailed 03/17/2005), Lip (Journal of Human Hypertension 14: 687-690, 2000), Bansal et al. (Journal of the Indian Medical Association 97: 226-233 (1999), Verhaar et al. (J. Hypertens 16: 45-50, 1998) and Nagy et al. (U.S. Patent No. 5,962,422) essentially for the reasons of record.

As indicated above in Section 12, given the extension of the election of species, newly added Wagner et al. teach the following.

Wagner et al. teach the use of PSGL-1 and chimeric constructs thereof (e.g., see paragraphs [0025]-[0036] and Claims) in the treatment of acute and chronic conditions associated with leukocyte adherence, inflammation and coagulation, including atherosclerosis and patients undergoing angioplasty, stenting procedures, atherectomy, bypass surgery or vessel-corrective techniques to aid in the prevention of restenosis (e.g., see paragraphs [0007]-[0012], [0015]-[0017], [0025], [0043] and Claims) as well as the administration and monitoring according to one of ordinary skill in the art and the needs of the patient (e.g., see paragraphs [0037]-[0047]).

Although the reference is silent about "hypertension" per se, appellant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Wagner et al. Further, the claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various conditions such as atherosclerosis and cardiovascular procedures (e.g., angioplasty) with PSGL-1 and fragments thereof and the properties of said PSGL-1 and fragments thereof at the time the invention was made.

Applicant's arguments, filed in the Brief on Appeal, filed 04/27/2007, and in the Reply Brief, filed 12/17/2007, have been fully considered but have not been found convincing essentially for the reasons of record.

As indicated previously, applicant's arguments, in conjunction with the Hemmerich 132 Declaration, filed 09/13/2006, and the examiner's rebuttal are essentially the same as of record.

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. See Schering Corp. v. Geneva Pharm. Inc., 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

When considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure.

There is no "manipulative difference in the method steps" between Cummings et al. and the claimed invention because both describe the administration of the same PSGL-1 to treat the same or nearly the same cardiovascular pathologies and conditions (including atherosclerosis and stroke (e.g., see Clinical Applications on columns 18-21).

Cummings et al. clearly teach that PSGL-1 would useful in the treatment of inflammatory and thrombotic disorders (e.g., see column 17, lines 60-63), in the inhibition of P-selectin-mediated interactions and leukocyte-mediated inflammation, which involved the activation of platelets and endothelium by thrombin and cytokines (e.g., see Clinical Applications on columns 18-21).

Cummings et al. clearly teach the role of platelet-leukocyte interactions in atherosclerosis, as it relates to atherogenesis (i.e., the formation of atheromas or atheromatous plaques, that is a deposit or degenerative accumulation of lipid-containing plaques, on the walls of arteries as in atherosclerosis) (e.g., see columns 19-20, overlapping paragraph).

Inhibiting thrombosis or atherogenesis in subject have hypertension would be an inherent result or benefit of Cumming's prophylactic administration of soluble PSGL- 1 to a patient with the same or nearly the same targeted diseases/conditions whether or not that benefit was recognized by Cummings et al.

It is irrelevant whether Cummings et al. methods were recognized in the art as treating or inhibiting thrombosis in subjects having hypertension, as long as treating or inhibiting "is the 'natural result flowing from' the explicit disclosure of the prior art".

As noted by the Introduction of Lip,
hypertension is/was a well-established risk factor for various diseases, including atherosclerosis and stroke and
the basic underlying pathophysiological processes underlying both of these major complication of hypertension are thrombogenesis and atherogenesis. (e.g., see Introduction of Lip).

In teaching Hypertension and Cerebrovascular Disease, newly added evidentiary reference Bansal et al. that several risk factors increase the chances of stroke but hypertension remain the single most important treatable risk factor in all age groups (e.g., see entire document, including Abstract and page 227, paragraph 2 and Conclusion).

In teaching that progressive vascular damage in hypertension is associated with increased levels of circulating P-selectin, newly added evidentiary reference Verhaar et al. conclude that selectins, including P-selectin are indicators of vascular damage in hypertension, based on investigations with different groups of hypertensives with varying degrees of vascular damage, including atherosclerotic patients (e.g., see entire document, including Abstract and Discussion).

In addition, newly added Nagy et al. provide for the therapeutic use of inhibitors that interfere with the binding of P-selectins for modulating the pathological consequences of a variety of conditions, including injury from ischemia and reperfusion, complications of surgery such as deep vein thrombosis, inflammatory conditions associated with cardiology such as restenosis and atheroclerosis (see entire document, including columns 22-25).

Applicant has <u>not</u> identified any manipulative difference between Cummings et al. methods and the claimed methods, and therefore have failed to establish that treating or inhibiting thrombosis patients having hypertension would not have naturally or inherently flowed
from practicing Cummings et al. methods to inhibit leukocyte-platelet interactions and P-selectin-mediated interactions in order to treat various inflammatory or thrombotic conditions or disorders, including atherosclerosis and stroke,
wherein the basic underlying pathophysiological processes underlying both of these major complication of hypertension are thrombogenesis and atherogenesis

Applicant further contends that there is no recognition in Cummings et al. that a P-selectin inhibitor can function to inhibit hypertension. This argument is not persuasive. Cummings et al. describes administration of the same P-selectin inhibitor required by the claims (PSGL-1), in the same amount. Again, it is irrelevant whether Cummings et al. recognized this particular natural or inherent result of the prior art methods to inhibit thrombosis in a subject having hypertension.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

While it is acknowledged that not all patients who have hypertension have atherosclerosis, strokes and ischemia-reperfusion injuries
and that not all patients who have atherosclerosis, strokes and ischemia-reperfusion injuries have hypertension,
clearly many/most, if not all, patients with atherosclerosis, strokes and ischemia-reperfusion injuries have complications due to hypertension.

Given that the prior art teaches treating all patients with atherosclerosis, strokes and ischemia-reperfusion injuries and
given that thrombus formation and hypertension were known complications of these patients;
the prior art methods clearly taught inhibiting thrombosis in subjects having hypertension.

Thrombus formation and hypertension were not considered insignificant, trivial nor irrelevant complications of atherosclerosis, strokes and ischemia-reperfusion injuries.

Under the broadest reasonable interpretation of the claims and consideration of applicant's intent, these claims are being read as "methods of treating / inhibiting" for prior art purposes.

Here, too, "preventing" and "prophylactically treating" would be considered methods of treating patients susceptible to thrombosis / deep vein thrombosis (e.g., a patient undergoing surgery, complications of hospitalization) as well as the nature of cardiovascular surgeries taught by Wagner et al. (e.g., angioplasty), as taught by the primary and secondary references.

The following is reiterated for applicant's convenience.

Cummings et al. teach the use of PSGL in the treatment of leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury, strokes and atherosclerosis (see column 18, paragraphs 5-8; columns 19-20, overlapping paragraph). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 3) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). The claimed functional limitations would be expected properties of the referenced methods of treating atherosclerosis with PSGL and fragments thereof.

Cummings et al. differs from the claimed PSGL by not disclosing particular human PSGL sequences and domain structure thereof. Larsen et al. teach the structure, including the domain structure and the use of PSGL-derived fragments which are the same or nearly the same as that claimed (see columns 9-15).

Larsen et al. teach the use of PSGL (e.g. ; columns 7-8, columns 13-18 and Examples), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P- or E-selectin mediated intercellular adhesion, such as myocardial infarction (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention).

Although Cummings et al. and Larsen et al. do not disclose all of the effective amounts recited in the instant claims 18-20, Cummings et al. and Larsen et al. teach the art known provision effective amounts of PSGL which inhibit P-selectin binding to treat thrombotic conditions to meet the severity of the condition and the needs of the patients. Therefore, the modes of administration and dosages encompassed by the claimed invention (claims 17-20) would have been met by the ordinary artisan at the time the invention was made to meet the severity of the conditions and the needs of the patients. For example, Larsen et al. also teach various modes of administration and dosing (e.g. pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician (columns 16-18).). Given the referenced treating of various acute and chronic conditions associated with thrombotic complications, it would have been inherent that such patients would have been identified as being subjects at risk of thrombosis.

The persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in the reference would have been intrinsically inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by Larsen et al. Although Cummings et al. and Larsen et al. do not disclose inhibiting hypertension and deep vein thrombosis by inhibiting P-selectin-PSGL-1 interactions per se, Blann et al., Araeneo et al. and DeFrees et al. all teach the role of such interactions in various thrombotic conditions, including hypertension and deep vein thrombosis at the time the invention was made.

Blann et al. teach that it was known that increased plasma levels of platelet specific products such as soluble P-selectin have been taken to imply increased platelet activation and that reversible platelet activation is present in hypertension (see entire document, including the Introduction). Blann et al. conclude that such changes associated with platelet activation may be partly responsible for the increases risk of thrombotic stroke and indicates that therapeutic strategies aimed at rescuing platelet activity may be beneficial (page 608, column 2, last paragraph).

Araneo et al. teach methods of preventing or reducing reperfusion injuries as well as ARDS, including preventing or reducing pulmonary hypertension via inhibiting the expression of P-selectin on endothelium (see entire document, including Summary of the Invention on columns 10-11 and Detailed Description of the Invention, including columns 11, 17 and Examples).

DeFrees et al. teach inhibitors of P-selectin-ligand interactions are especially useful in minimizing tissue damage that accompanies thrombotic disorders, including having therapeutic value in treating patients with stoke, myocardial infarctions, deep vein thrombosis and pulmonary embolism (see entire document, including column 45, paragraph 2).

As pointed out previously, it has been noted that treating "atherosclerosis" is consistent with the instant specification (see pages 6-7, overlapping paragraph of the instant specification and the Section on Prophylactic And Therapeutic Methods on page 32 of the instant specification).

Further, The Merck Manual notes that arterial hypertension is a complication of atherosclerosis, cerebrovascular insufficiency with stroke and renal failure (see page 1632, Symptoms and Signs; see Atherosclerosis on pages 1654 - 1658, including page 1656, Hypertension; Cerebrovascular Disease on pages 1417-1424).

As noted by Lip, Journal of Human Hypertension,
"hypertension is well-recognized to be an important contributor to heart attacks and stroke" and that "hypertension it thrombotic in nature".
See entire document, particularly the Introduction on page 687.

This is consistent with the disclosure on page 1, paragraph 3 in the Background of the Invention of the instant specification notes that:
"Moreover, one of the basic pathophysiological processes underlying the major complications of hypertension (i.e. heart attack and stroke) is thrombogenesis (Lip (2000) J Hum Hypertension 14:687)."

As pointed out previously, and consistent with the Background of the Invention and disclosure of the instant specification concerning hypertension,
the Merck Manual notes that
"Hypertension is the most important risk factor predisposing to stroke";
"It is one of three risk factors, along with cigarette smoking and hypercholesterolemia predisposing to coronary atherosclerosis";
(see Prognosis on page 1634, column 1.

"Hypertension is a more important risk factor for stroke than for atherosclerotic heart disease
(see page 1632, column 1, paragraph 1 of Pathology); and
"Heart failure, symptomatic coronary atherosclerosis, cerebrovascular disease and renal failure require urgent and judicious antihypertensive therapy
(see page 1634, column 2, paragraph 1 of Antihypertensive drug therapy).

On this record, it is reasonable to conclude that the same patient(s) is (are) being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that appellant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Although Cummings et al. and Larsen et al. do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made.

With respect to the role of LTC_4 in thrombus formation and thrombotic conditions, the following is noted.

Cummings et al. and Larsen et al. differ from the claimed methods by the claimed methods by not disclosing the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions as taught by Maugeri et al. and

Maugeri et al. teach that is was known at the time the invention was made that LTC_4 was one of the biologically active substances that play a role in inflammation and thrombosis (see entire document). Further, Maugeri et al. teach that anti-P-selectin antibodies can inhibit LTC_4 production (see Abstract, Results and Discussion). Further, Marugeri et al. discuss that neutrophil-platelet interaction via P-selectin plays a role in LTC_4 cooperative synthesis, which play a significant role in sever pathophysiological situations including inflammatory and cardiovascular diseases (see Abstract, Results and Discussion).

Johnston et al. teach that anti-P-selectin antibodies can inhibit inflammatory conditions, including LTC_4 induced leukocyte rolling in vivo (see entire document, including Abstract, Results and Discussion).

Again, although Cummings et al. and Larsen et al. do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions, as evidenced by Maugeri et al. and Johnston et al. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made. Further, both Maugeri et al. And Johnston et al. teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including LTC_4.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions.

Given the teachings of Cummings et al. and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary / thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses.

Given the role and indication of P-selectin in platelet activation and various thrombotic disorders and the clear teaching of the prior art to target such platelet activation via P-selectin, such targeted conditions and disorders would have included hypertension, including pulmonary hypertension associated with ARDS as well as deep vein thrombosis, as taught by Blann et al., Araneo et al., DeFrees et al., The Merck Manual and Lip et al.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Given that the claims drawn to the methods of treating deep vein thrombosis have been acted upon in the instant application, the following New Grounds of Rejection have been set forth to provide further support for the obviousness of treating said condition with PSGL-1 at the time the invention was made.

Even though these New Grounds of Rejection are set forth, it does not appear that applicant has argued treating deep vein thrombosis separately from the basic methods of treating or inhibiting thrombosis in a subject having hypertension (e.g., see Claim 1).

15. Claims 1-20, 25-40 and 43-57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. Patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) AND Wagner et al. (US 2002/0040008)
in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207)
and in further evidence of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999) (892 mailed 03/17/2005), Lip (Journal of Human Hypertension 14: 687-690, 2000) and Bansal et al. (Journal of the Indian Medical Association 97: 226-233 (1999) Verhaar et al. (J. Hypertens 16: 45-50, 1998) and Nagy et al. (U.S. Patent No. 5,962,422) essentially for the reasons of record
as applied to the claims 1-20, 25-40 and 43-57 above for the reasons of record and addressed above
and further in view of by Eppihimer et al. (Journal of Leukocyte Biology (Suppl.): 27, 1999) (1449; #E2) AND/OR (Downing et al., J. Vasc. Surg 25: 816-828, 1997) (1449; #A12) and in further evidence of Stephens et al. (U.S. Patent No. 5,688,935) and The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999; see pages 593-601 and 1792-1794).

As disclosed on page 6, paragraph 2 of the instant specification, thrombosis includes deep vein thrombosis (DVT), which is the formation of a thrombus within a deep vein, such as in the legs.

To prevent further accrual and formation of new clots with a risk of pulmonary embolism, the ordinary artisan employed efforts to inhibit such deleterious thromboembolic complications.

Eppihimer et al. teach the role of recombinant forms of PSGL-1 in the treatment of deep vein thrombosis (see Abstract).

Downing et al. teach that the P-selecting inhibitor anti-P-selectin antibody reduced the incidence of thrombus, venous wall cytokine levels and gadolinim enhancement, a measure of vascular injury in the pathogenesis of deep vein thrombosis (see entire document) and teach the knowledge and value of inhibiting the interactions among leukocytes, endothelial cells and platelet in clinically reducing subsequent vein wall injuries and resultant complications (see Discussion and Conclusion).

Stephens et al. provide further evidence of the relationship between hypertension and deep vein thrombosis by noting that arises as a complication of deep vein thrombosis and patients with pulmonary embolism carry significant hypertension (see entire document, particularly column 14, paragraph 1).

Also, The Merck Manual of Diagnosis and Therapy describes the Etiology and Pathogenesis of pulmonary embolism resulting from migration of a thrombus from a leg or pelvic vein and the role of pulmonary hypertension in such patients (e.g., see Pulmonary Embolism on pages 593-601 and Venous Thrombosis on pages 1792-1794)

As indicated above, newly added Nagy et al. provide for the therapeutic use of inhibitors that interfere with the binding of P-selectins for modulating the pathological consequences of a variety of conditions, including injury from ischemia and reperfusion, complications of surgery such as deep vein thrombosis, inflammatory conditions associated with cardiology such as restenosis and atheroclerosis (see entire document, including columns 22-25).

Given the teachings of Eppihimer et al. OR Downing et al. concerning the role of P-selectin antagonists in the treatment of deep vein thrombosis, including the evidence of Stephens and The Merck Manual concerning the role or resultant hypertension of such complications as well as the teachings of Cummings et al. and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary / thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit deep vein thrombosis, including patients with hypertension via the inhibition of PSGL-1-mediated interactions and inflammatory responses.

Given the role and indication of P-selectin in platelet activation and various thrombotic disorders and the clear teaching of the prior art to target such platelet activation via P-selectin, such targeted conditions and disorders would have included hypertension, including pulmonary hypertension associated with ARDS as well as deep vein thrombosis, as taught by Blann et al., Araneo et al., DeFrees et al., The Merck Manual and Lip et al.

Under the broadest reasonable interpretation of the claims and consideration of applicant's intent, these claims are being read as "methods of treating / inhibiting" for prior art purposes. Here, too, "preventing" and "prophylactically treating" would be considered methods of treating patients susceptible to thrombosis / deep vein thrombosis (e.g., a patient undergoing surgery, complications of hospitalization), as taught by the secondary references.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claim 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. patent No. 5,464,778) AND Larsen et al. (U.S. Patent No. 5,840,679) and Wagner et al. (US 2002/0040008)

in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348) and DeFrees et al. (U.S. Patent No. 5,604,207) and in further evidence of The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999), Lip (Journal of Human Hypertension 14: 687-690, 2000) and Bansal et al. (Journal of the Indian Medical Association 97: 226-233 (1999), Verhaar et al. (J. Hypertens 16: 45-50, 1998) and Nagy et al. (U.S. Patent No. 5,962,422) essentially for the reasons of record

as applied to claims 1-20, 25-27, 29-40, 45 and 50-57 above

and in further evidence of Maugeri et al. (Thrombosis and Haemostasis 72: 450-456, 1994) and Johnston et al. (J. Immunol. 159: 4514-4523, 1997) essentially for the reasons of record.

As pointed out above, the applicant's Reply Brief, filed 12/17/2007, noted that the Examiner's Answer did not state the rejection of claim 27 under 35 USC 103(a) as unpatentable over Cummings, Larsen, Blann, Araneo, DeFrees, the Merck Manual, Lip further in view of Maugeri and Johnston stands.

Other than the addition of Bansal et al. (Journal of the Indian Medical Association 97: 226-233 (1999) to the base rejection,

applicant's arguments and the examiner's rebuttal are essentially the same of record.

In addition, newly added Nagy et al. provide for the therapeutic use of inhibitors that interfere with the binding of P-selectins for modulating the pathological consequences of a variety of conditions, including injury from ischemia and reperfusion, complications of surgery such as deep vein thrombosis, inflammatory conditions associated with cardiology such as restenosis and atherosclerosis (see entire document, including columns 22-25).

The following of record is reiterated for applicant's convenience.

Applicant's arguments in conjunction with the Hemmerich Declaration under 37 CFR 1.132, filed 9/13/06, have been fully considered but have not been convincing essentially for the reasons of record and that addressed herein /above.

Applicant / Declarant submit that the prior art, including both Maugeri and Johnston, does not explicitly or impliedly provide sufficient motivation and expectation of success in arriving at applicant's invention.

The teachings of Cummings et al. and Larsen et al. in further view of Blann et al. (Journal of Human Hypertension 11: 607-609, 1997), Araneo et al. (U.S. Patent No. 6,150,348), DeFrees et al. (U.S. Patent No. 5,604,207) and The Merck Manual of Diagnosis and Therapy, Seventeenth Edition are set forth above and are of record.

Cummings et al. and Larsen et al. differ from the claimed methods by the claimed methods by not disclosing the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions as taught by Maugeri et al.

While applicant / Declarant acknowledge that Maugeri speculates about the importance of P-selectin-mediated interactions for the production of LTC4,

applicant / Declarant submit that this reference not teach nor suggest a relationship between thrombosis formation and hypertension nor methods of treating or inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering P-selectin ligand to said subjects.

While applicant / Declarant acknowledge that Johnston investigates the ability of anti-P-selectin antibody to inhibit LTC4-induced leukocyte rolling and speculates about anti-inflammatory strategies,

applicant / Declarant submit that this reference does not identify the use of P-selectin protein, nor the relationship between thrombosis and hypertension

Here again and as pointed out previously and in contrast to applicant's assertions of lack of relevant teachings, Maugeri et al. teach that is was known at the time the invention was made that LTC_4 was one of the biologically active substances that play a role in inflammation and thrombosis (see entire document). Further, Maugeri et al. teach that anti-P-selectin antibodies can inhibit LTC_4 production (see Abstract, Results and Discussion). Further, Marugeri et al. discuss that neutrophil-platelet interaction via P-selectin plays a role in LTC_4 cooperative synthesis, which play a significant role in sever pathophysiological situations including inflammatory and cardiovascular diseases (see Abstract, Results and Discussion).

In addition, Johnston et al. teach that anti-P-selectin antibodies can inhibit inflammatory conditions, including LTC_4 induced leukocyte rolling in vivo (see entire document, including Abstract, Results and Discussion).

Again, although Cummings et al. and Larsen et al. do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions per se, LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions, as evidenced by Maugeri et al. and Johnston et al.. Therefore, one of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by Cummings et al. and Larsen et al. would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made. Further, both Maugeri et al. and Johnston et al. teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including LTC_4.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer PSGL-1, fragments and chimeric constructs thereof, provided they had the properties of inhibiting PSGL-1-mediated interactions and inflammatory responses, as taught by Cummings et al. and Larsen et al. to treat patients with various thrombotic conditions. Given the teachings of Cummings et al. and Larsen et al. to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents, as properties of such treatment of PSGL-1-mediated interactions and inflammatory responses.

Given the role and indication of P-selectin in platelet activation and various thrombotic disorders and the clear teaching of the prior art to target such platelet activation via P-selectin, such targeted conditions and disorders would have included hypertension, including pulmonary hypertension as well as deep vein thrombosis, as taught by Blann et al., Araneo et al. and DeFrees et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Once again, it is noted that once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the prior art pertain to inhibiting P-selectin : PSGL-1 mediated and / or platelet-mediated interactions and functions in the treatment of various conditions and diseases associated or linked with hypertension and indicate success in administering PSGL to treat such conditions and diseases to solve a similar problems associated with the above-mentioned conditions and diseases would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

Applicant's arguments have not been found persuasive.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-800.

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